Remarks/Arguments:

Following entry of the above amendment, claims 1-8, 10-18 and 20 are pending. Claims 1, 5, and 11 have been amended in response to objections and rejections raised by the Examiner. Specifically, claims 1 and 11 have been amended to provide the proper antecedent basis for "ribonucleoside triphosphates" and also to include the limitation of "removing the nucleic acid template from the incubated reaction mix". Support for the limitation of "removing the nucleic acid template from the incubated reaction mix" can be found throughout the specification, for example, on page 3, line 33. Claim 5 has been amended to recite "DNA primase" which was inadvertently left out when the claim was drafted. Claims 6 and 16 have been amended to remove the Trademark names of SYBR Green II, RiboGreen, and YO-PRO-1, which are all well known types of cyanine dyes and "cyanine dye" has been inserted into the claim instead. No new matter has been added by this amendment.

Claim objections

Claim 5 has been amended to correct the typographical error of the omission of "DNA primase" after *S. aureus*. This amendment obviates the rejection of this claim.

35 U.S.C. § 112

Claims 1-8, 10-18 and 20 have been rejected because the limitation "the triphosphates" has insufficient antecedent basis. Applicants have amended the claim to recite "the ribonucleoside triphosphate", which limitation has sufficient antecedent basis.

Claims 6 and 16, which contain trademark names, have been amended to use the generic name of cyanine dye.

Applicants respectfully request withdrawal of the rejection.

35 U.S.C. § 103

The present invention is directed to a method for determining DNA primase activity and for identifying compounds that modulate DNA primase activity. The assays of the present invention are based upon the interaction between RNA and a fluorescent reagent that generates a fluorescent signal. Applicants have found that that there is a linear relationship between the

fluorescent signal and the concentration of RNA synthesized by DNA primase even in the presence of the DNA template (Figure 1). Thus, it is not necessary to remove the template or to isolate the RNA product. (see page 3, lines 27-34).

The Examiner has rejected claims 1-6, 8, 10-16 18 and 20 as being obvious over Sivaraja (US 6,042,038) and Jones et al. (Analytical Biochemistry (1998) 265:368-374).

In establishing a prima facie case of obviousness, the office must show that the prior art contains: 1) the motivation to modify a reference, or to combine references, to arrive at the claimed invention, 2) a reasonable expectation of success, and 3) a teaching or suggestion of all the claimed limitations.

Sivaraja teaches a high-throughput screening assay for primase activity. Sivaraja teaches two methods: a solution phase method and a solid phase method. In the solution phase method (see column 10, line 6 to column12, line 55) the DNA-RNA heterohybrid once formed should be immobilized or captured on a solid phase, either directly or indirectly, thereby separating the heterohybrid from the reaction mix. In the solid phase method, a nucleic acid template is first immobilized to a solid support prior to exposure to DNA primase (see column 12, line 57 to column 13, line 36). Sivaraja teaches that in the detection step the "DNA-RNA heterohybrid regions synthesized by the primase is typically washed free of unbound components" (see column 16, lines 20-25). There is no suggestion in Sivaraja of being able to detect the polymerized product without first separating the product from the reaction mixture. Moreover, there is no teaching in Sivaraja that the polymerized product can be detected directly. Thus a skilled person following the teaching of Sivaraja would not be motivated to perform an assay where the polymerized product was not first separated from the reaction mixture as a person skilled in the art would reason that it would be impossible to get a readout from the assay. Thus, Sivaraja fails completely to provide any suggestion or motivation to make the claimed invention.

As Sivaraja alone is insufficient to provide the needed suggestion or motivation to make the claimed invention, we turn to the combination of references relied on by the Examiner, namely Sivaraja and Jones et al. to determine whether Jones et al. can supply what Sivaraja lacks.

Jones et al. disclose the characteristics of the dye RiboGreen in its application for RNA quantitation using fluorescence based solution assays. In one of the various experiments performed by Jones et al., Jones et al investigated whether the presence of other nucleic acids would interfere with the RiboGreen fluorescent response. Jones et al. found that RiboGreen exhibited strong fluorescence enhancement upon binding to double-stranded DNA, and

concluded that the presence of DNA in mixed nucleic acid samples "***interferes***" with RNA quantitation (see page 372, last paragraph of section entitled "Assay response to various nucleic acids"). Thus, one skilled in the art would not have been motivated to combine the teachings of Sivaraja with Jones et al. and arrive at the present invention because Jones et al. teach a person skilled in the art that when using Ribogreen to quantitate RNA in a sample containing DNA there is no reasonable expectation of successfully quantiting the RNA in the sample because of the interference in quatitation caused by the presence of the DNA.

Moreover, Jones et al. teach away from detecting RNA in the presence of DNA by suggesting that if DNA is present in the sample, RNase-free DNase I should be added to the sample in order to remove the interfering DNA and have an RNA-selective assay (see page 372, last paragraph of section entitled "Assay response to various nucleic acids"). In the claimed method of the present invention, the RNA is quantitated directly without further steps of separating the RNA product from the incubated reaction mix or removing the nucleic acid template from the incubated reaction mix. Since Jones et al. teach that the presence of DNA interferes with RNA quantitation and should be removed, one skilled in the art based on the prior art would not expect to be able to successfully quantitate RNA as in the claimed method because the incubation mix of the present method contains DNA.

Given that the primary reference, Sivaraja, provides no teaching that the RNA can be detected without first separating the RNA from the reaction mixture, and that Jones et al. teach that DNA interferes with RNA quatitation when using a fluorescent marker, this combination of references cannot render obvious the present invention. Thus, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Claims 7 and 17 are rejected over Sivaraja (as above), in view of Jones et al. (as above) and further in view of Khopde et al. (Biochemistry (2002) 41: 14820-14830 and further in view of Sheaff et al. (biochemistry (1993) 32: 3027-3037) and further in view of Tseng et al. (The Journal of Biological Chemistry (1982) 257(13): 7280-7283).

Claims 7 and 17, which depend from claims 1 and 11, respectfully, are directed to an exemplary nucleic acid template of SEQ ID NO:1. As discussed above, the combination of Sivaraja and Jones et al. fail to make the invention of independent claims 1 and 11 obvious. The references of Khopde, Shaeff et al., and Tseng et al. do not overcome the deficiencies of Sivaraja and

Jones et al. Khopde et al. is cited for teaching the trinucleotide CTG and for using the oligonucleotide d(CTGCAAAGC); Shaeff et al. is cited for using an oligonucleotide comprising d(TC)30 and Tseng et al. is cited for teaching poly(dCdT) templates for monitoring DNA primase activity. However, none of these secondary references supply any teaching or suggestion relating to a method for detecting DNA primase activity by detecting directly the RNA with a fluorescent marker that binds the RNA, wherein the detecting step requires no further steps of separating the RNA product from the incubated reaction mix or removing the nucleic acid template. Therefore, the further combination of Khopde, Shaeff et al., and Tseng fail to make obvious the invention of claims 1 or 11, or any claim that depends therefrom.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejections for obviousness.

Conclusion

On the basis of the foregoing amendment and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and a Notice of Allowance for the pending claims is respectfully requested.

A petition for a three-month extension of time is being filed herewith, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 100998-1P US.

Although Applicants believe no other fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 100998-1P US.

Respectfully submitted,

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